Very Early Nimodipine Use in Stroke (VENUS)
A Randomized, Double-Blind, Placebo-Controlled Trial

J. Horn, MD; R.J. de Haan, PhD; M. Vermeulen, MD, PhD; M. Limburg, MD, PhD

Background and Purpose—The Very Early Nimodipine Use in Stroke (VENUS) trial was designed to test the hypothesis that early treatment with nimodipine has a positive effect on survival and functional outcome after stroke. This was suggested in a previous meta-analysis on the use of nimodipine in stroke. However, in a recent Cochrane review we were unable to reproduce these positive results. This led to the early termination of VENUS after an interim analysis.

Methods—In this randomized, double-blind, placebo-controlled trial, treatment was started by general practitioners or neurologists within 6 hours after stroke onset (oral nimodipine 30 mg QID or identical placebo, for 10 days). Main analyses included comparisons of the primary end point (poor outcome, defined as death or dependency after 3 months) and secondary end points (neurological status and blood pressure 24 hours after inclusion, mortality after 10 days, and adverse events) between treatment groups. Subgroup analyses (on final diagnosis and based on the per-protocol data set) were performed.

Results—At trial termination, after inclusion of 454 patients (225 nimodipine, 229 placebo), no effect of nimodipine was found. After 3 months of follow-up, 32% (n = 71) of patients in the nimodipine group had a poor outcome compared with 27% (n = 62) in the placebo group (relative risk, 1.2; 95% CI, 0.9 to 1.6). A treatment effect was not found for secondary outcomes and in the subgroup analyses.

Conclusions—The results of VENUS do not support the hypothesis of a beneficial effect of early nimodipine in stroke patients. (Stroke. 2001;32:461-465.)

Key Words: calcium channel blockers ■ cerebrovascular disorders ■ nimodipine ■ randomized controlled trials

No effective neuroprotective treatment is available in ischemic stroke. Administration of agents that antagonize the influx of calcium ions by way of voltage-sensitive calcium channels can reduce infarct size in animal experiments.1 In 1988 a randomized, placebo-controlled trial in stroke patients showed a significant reduction of death and neurological impairment after administration of the calcium antagonist nimodipine.2 Similar results were found in subarachnoid hemorrhage, in which the administration of nimodipine before onset of ischemia was associated with a reduced occurrence of cerebral ischemia and improved clinical outcome.3,4 Further randomized studies with nimodipine or other calcium antagonists (eg, flunarizine, isradipine) in ischemic stroke did not confirm the beneficial effect of the earlier study.5–8 However, subgroup analyses by the American Nimodipine Study Group of patients treated with nimodipine within 18 hours after stroke onset in the American Nimodipine Trial suggested improved outcome after treatment.5 The notion that a short time interval between stroke onset and start of treatment is crucial was supported by results of a meta-analysis of 9 trials with nimodipine in ischemic stroke.9 Although the overall analysis did not show any beneficial effect, a statistically significant reduction of poor outcome favoring nimodipine was present for patients treated within 12 hours after stroke onset (odds ratio, 0.62; 95% CI, 0.44 to 0.87). For treatment between 12 to 24 hours no effect was demonstrated, whereas after 24 hours nimodipine was associated with worse outcome. Since any subgroup analysis showing a beneficial effect should be interpreted with caution because there is always the danger that it may be a chance finding,10 we decided to prospectively study the effects of nimodipine administered early after stroke onset: the Very Early Nimodipine Use in Stroke (VENUS) study.

Subjects and Methods

Patient Selection

Patients with acute stroke and hemiparesis were included in this randomized, double-blind, placebo-controlled trial by the first physician encountered. In the Netherlands this is in most cases the general practitioner or, less often, the neurologist. To enable general practitioners to randomize patients meant that the design of the trial had to be simple. Data and time needed to complete the case record form had to be limited and inclusion and exclusion criteria straightforward. Written or witnessed oral informed consent was required. When this was impossible, informed consent by proxy was allowed. Procedures followed were in accordance with the ethical standards of

Received July 20, 2000; final revision received October 13, 2000; accepted October 19, 2000.

From the Departments of Neurology (J.H., M.V., M.L.), Clinical Epidemiology and Biostatistics (R.J. de H.), and Medical Informatics (M.L.), Academic Medical Center, University of Amsterdam (Netherlands).

Correspondence to M. Limburg, PO Box 22700, 1100 DE, Amsterdam, Netherlands. E-mail m.limburg@amc.uva.nl

© 2001 American Heart Association, Inc.

Stroke is available at http://www.strokeaha.org

461
the Helsinki Declaration. The study was approved by the Dutch general practitioners ethics committee and local ethics committees.

Exclusion Criteria
Exclusion criteria included ability to raise arm or leg >10 seconds against gravity; inability to start treatment within 6 hours; age <18 or >85 years; previous participation in this trial; pregnancy; impaired consciousness (did not obey orders and did not open eyes on painful stimuli); other diseases likely to cause death within 1 year; previous stroke, resulting in serious handicap (Modified Rankin Scale score >3); dysphagia, excluding oral medication at trial onset; systolic blood pressure <130 mm Hg; heart rate <50 bpm; and ≥3 of the following 4 conditions: severe headache, vomiting, hypertension (systolic blood pressure >220 mm Hg), and use of oral anticoagulants.

Intervention
Trial medication consisted of tablets containing 30 mg oral nimodipine or placebo, administered every 6 hours for 10 days. Medication was provided by Bayer AG. Any other concomitant medication, except nimodipine, was allowed. Medication was randomized in equal blocks of 10, according to computer-generated lists. Numbered boxes contained one complete treatment or identical placebo course and were sequentially distributed among participating general practitioners and neurologists.

Outcome Assessment
The primary end point was poor outcome, defined as all-cause mortality or dependency in daily life (Modified Rankin Scale score >3).11 3 months after inclusion. This cutoff point for the Modified Rankin Scale was chosen because patients with a Rankin score of 4 or 5 almost certainly cannot live independently.12 Secondary end points were neurological status and blood pressure 24 hours after inclusion, mortality after 10 days, and adverse events. Outcome was assessed in telephone interview by a trained data manager nurse, blinded for treatment allocation. We attempted to interview the patient; when this was impossible, the primary caregiver was interviewed. Assessment of functional outcome after stroke by telephone interview was established to be reliable.13,14

Data Collection
The following data were collected at inclusion: sex, age, comorbidity (previous stroke, cardiac disease, other diseases), level of activities of daily life before stroke (independent, in need of some help, dependent), severity of hemiparesis (raise arm or leg for 10 seconds against gravity), level of consciousness, aphasia, and whether the patient was admitted to a hospital for the present stroke. After 24 hours the following data were recorded: neurological status (improved, unchanged, or deteriorated as judged by the treating physician) and systolic and diastolic blood pressures. Ten days after inclusion, data on mortality and adverse events were collected. The following data were collected at the end of follow-up (3 months): diagnosis (ischemic stroke, hemorrhagic stroke, no radiological investigation, other diagnosis), mortality, level of dependency (assessed with the Modified Rankin Scale11), and adverse events.

Interobserver Variability on Primary Outcome Assessment and External Validity
To assess interobserver agreement on the Modified Rankin Scale at the end of follow-up, 116 consecutive patients were called again (1 day later) by a second trial nurse. Since a large group of general practitioners participated, it was impossible to perform on-site audits. However, we closely followed 117 randomly selected general practitioners during 6 months to assess external validity. Each general practitioner was contacted monthly to assess the number of encountered and included stroke patients and reasons for not including patients (exclusion criteria or other reasons).

Group Size
We planned to include 1500 patients on the basis of the following assumptions: 80% power, 2-tailed significance level of 5%, reduction of poor outcome from 40% (placebo group) to 32% (treatment group), leading to 575 patients in each treatment arm. Because prehospital trial inclusion by general practitioners was likely to lead to inaccurate diagnosis and drug noncompliance, we substantially raised the estimated sample size by 30%.

After inclusion of 454 patients the trial was terminated early. In our Cochrane Collaboration review on calcium antagonists for ischemic stroke, the positive effects of the early administration of nimodipine could not be confirmed,13 which led to an interim analysis by an independent committee. The data of the systematic review and this trial showed that the assumptions on which the sample size was calculated were unrealistic. Inclusion was stopped, and results thus far are presented here.

Statistical Analysis
Analysis was by intention to treat. The main analyses focused on comparisons of the primary end point (poor outcome) and secondary end points (neurological status and blood pressure 24 hours after inclusion, mortality after 10 days, and adverse events) between the trial medication groups. Subgroup analyses addressed the effect of nimodipine on poor outcome in patients with definite ischemic strokes (CT scan exclusion of hemorrhage), hemorrhagic strokes (CT scan confirmation of intracranial hemorrhage), patients in whom no CT scan was made, and per-protocol analysis. Effect sizes were expressed in relative risk (RR) estimates with 95% CIs with the exception of differences in blood pressures (unpaired t test), neurological status, and adverse events (χ² tests). Interobserver agreement of the outcome assessment was calculated with κ statistics.16

Results
At the time of the interim analysis (July 1998), 454 patients were randomized; 225 received nimodipine, and 229 received placebo. Baseline characteristics of both groups are presented in Table 1. There were more patients with previous stroke,
aphasia, and a diagnosis other than stroke in the placebo group. Furthermore, it should be noted that the general practitioner’s diagnosis of stroke was correct in 98% of all patients.

Main Analyses: Primary and Secondary Outcomes
The results of the outcome assessments are presented in Table 2. After 3 months, 71 patients (32%) in the nimodipine-treated group had a poor outcome compared with 62 (27%) in the placebo-treated group. This yielded an RR of 1.2 (95% CI, 0.9 to 1.6). In both treatment arms, functional outcome could not be assessed in 3 patients.

Twenty-four hours after randomization, no significant differences in neurological status or blood pressure readings were present between the 2 treatment groups. After 10 days, 14 patients (6%) had died in the nimodipine group compared with 20 (9%) in the placebo group. This difference was not statistically significant (RR, 0.7; 95% CI, 0.4 to 1.4). Adverse reactions were reported by 31 patients. Trial medication was stopped in 15 patients (7 nimodipine, 8 placebo); treatment allocation was never broken.

Subgroup Analyses
In patients with definite ischemic strokes (n=261), a borderline significant adverse effect of nimodipine on poor outcome was present (RR, 1.4; 95% CI, 1.0 to 2.1), whereas in patients with intracranial hemorrhages (n=35) and patients without radiological investigations (n=150), no differences could be demonstrated. In the per-protocol analysis (n=345), RR for poor outcome was 1.2 (95% CI, 0.8 to 1.6). These data are presented in Table 3.

Interobserver Agreement on Primary Outcome Assessments and External Validity
Interobserver agreement was determined in 116 patients. The agreement was almost perfect (κ=0.94). The 117 general practitioners whom we closely monitored for assessment of

### Table 2. Results of Outcome Assessment

<table>
<thead>
<tr>
<th>Analyses</th>
<th>Nimodipine (n=225)</th>
<th>Placebo (n=229)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor outcome at 3 mo</td>
<td>71 (32%)</td>
<td>62 (27%)</td>
<td>RR, 1.2; 95% CI, 0.9–1.6</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurological status after 24 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved</td>
<td>112</td>
<td>125</td>
<td></td>
</tr>
<tr>
<td>Unchanged</td>
<td>68</td>
<td>54</td>
<td>P=0.35†</td>
</tr>
<tr>
<td>Deteriorated or death</td>
<td>39</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>6</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Blood pressure after 24 h, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean systolic</td>
<td>153</td>
<td>152</td>
<td>P=0.83‡</td>
</tr>
<tr>
<td>Mean diastolic</td>
<td>84</td>
<td>86</td>
<td>P=0.20‡</td>
</tr>
<tr>
<td>Death at 10 d</td>
<td>14 (6%)</td>
<td>20 (9%)</td>
<td>RR, 0.7; 95% CI, 0.4–1.4</td>
</tr>
<tr>
<td>Adverse events*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Bradycardia</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>2</td>
<td>4</td>
<td>P=0.49†</td>
</tr>
<tr>
<td>Frequent micturation</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Nasal bleeding</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Skin rash</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

*Patients could report more adverse events.
†χ² test.
‡Unpaired t test.

### Table 3. Subgroup Analyses of Patients With Poor Outcome in Each Group

<table>
<thead>
<tr>
<th></th>
<th>Nimodipine</th>
<th>Placebo</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke</td>
<td>n=133</td>
<td>n=128</td>
<td>1.4</td>
<td>1.0–2.1</td>
</tr>
<tr>
<td>Poor outcome at 3 mo</td>
<td>44 (34)</td>
<td>30 (24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>n=20</td>
<td>n=15</td>
<td>1.0</td>
<td>0.6–1.7</td>
</tr>
<tr>
<td>Poor outcome at 3 mo</td>
<td>11 (58)</td>
<td>9 (60)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No CT scan</td>
<td>n=71</td>
<td>n=79</td>
<td>0.8</td>
<td>0.5–1.5</td>
</tr>
<tr>
<td>Poor outcome at 3 mo</td>
<td>16 (23)</td>
<td>21 (27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per protocol*</td>
<td>n=179</td>
<td>n=168</td>
<td>1.1</td>
<td>0.8–1.6</td>
</tr>
<tr>
<td>Poor outcome at 3 mo</td>
<td>56 (31)</td>
<td>47 (28)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are number (%) unless indicated otherwise.

*107 patients were excluded from this analysis because of the following exclusion criteria: 8, other diagnosis; 74, hemiparesis not severe enough; 8, age >85 years; 10, swallowing disturbance; and 7, other exclusion criteria.
extensive validity encountered 73 stroke patients during a 6-month period. Six of these 73 (8%) were entered into the study. Of the remaining 67 patients, 44 were not included because of exclusion criteria (parese not severe enough [n=16], existence of symptoms >6 hours [n=14], age >85 years [n=12], and other [n=2]). In 23 cases the general practitioners simply forgot VENUS or were uncertain.

Discussion
The possibility that agents reducing influx of calcium ions through voltage-sensitive calcium channels may improve outcome after ischemic stroke has led to clinical trials in which at least 7665 patients have been included. Although nimodipine has never been used on a large scale in Western countries, reported beneficial effects led to the introduction of nimodipine in clinical practice in some other countries. For instance, in China 88% of physicians caring for stroke patients reported the use of nimodipine occasionally or routinely.

VENUS was started to test the hypothesis that early administration of nimodipine is effective, as suggested in a subgroup analysis of a previous meta-analysis. In this subgroup analysis, data of 616 patients (from 6 hospital-based trials) treated within 12 hours after stroke onset yielded a statistically significant beneficial effect of nimodipine for neurological outcome (odds ratio, 0.62; 95% CI, 0.44 to 0.87). Similar findings were reported for functional outcome. This positive result could not be reproduced in our systematic review, in which (before the VENUS data were added) data of 825 patients from 10 trials were included (odds ratio, 0.91; 95% CI, 0.68 to 1.21). This interim analysis of VENUS results was performed by an independent interim committee. This committee reported that on the basis of data from our systematic review and the results of VENUS thus far, the assumptions on which the sample size was calculated were unrealistic; the committee therefore advised that inclusion be stopped. The steering committee decided to terminate the trial; by that time 454 patients were included. This small number of patients increases the risk of a type II error. However, the results of this trial are in concordance with the results from our Cochrane review, in which an RR of poor outcome after early treatment with nimodipine of 1.0 was found (95% CI, 0.9 to 1.2).

The VENUS trial did not show a beneficial effect of oral nimodipine administered within 6 hours of stroke. In contrast to previous nimodipine trials, VENUS was performed in a primary care setting. The safety profile of nimodipine allows treatment immediately after stroke onset, before hospital admission. An effective neuroprotective agent could hypothetically be beneficial for patients with parenchymal cerebral hemorrhage, since the area surrounding the hemorrhage is ischemic because of increased pressure. However, trials with general practitioners have their limitations. The design must be simple and straightforward, and inclusion is performed by relatively inexperienced physicians. By excluding patients who were able to raise their arm or leg >10 seconds against gravity, we tried to prevent inclusion of patients who had no stroke. This may have led to a selection bias, including mainly patients with severe stroke and excluding patients with small lacunar (sensory stroke) or cerebellar infarctions. Most specific stroke scales cannot be assessed by untrained general practitioners and were therefore not used in VENUS. We encouraged the participating general practitioners to refer included patients to a neurologist for diagnostic investigations. A CT or MRI scan was made in only 68% of all included patients. The diagnosis of stroke was correct in 98% of patients in which diagnosis was established by CT or MRI scan. Participating general practitioners included 8% of stroke patients for whom they were consulted. Most patients were excluded correctly, according to predefined exclusion criteria, but in a considerable number of stroke patients (32%), the general practitioner forgot about the trial or was uncertain about the diagnosis. A comparable trial with prehospital thrombolysis of patients with suspected acute myocardial infarction had a significantly higher inclusion rate (60%). No other prehospital stroke trials exist with which to compare our data, but in the American Nimodipine Trial (an acute stroke trial in a hospital setting) the inclusion rate was similar (7.9%). The relative inexperience of general practitioners and acute stroke trials may affect the inclusion rate negatively. Furthermore, even general practitioners will not see all stroke patients within 6 hours after onset of symptoms. Patients’ delay definitely seems to play a role.

Other promising neuroprotective agents have recently been reported to be ineffective in improving outcome after ischemic stroke. Despite the limitations caused by the trial design of VENUS and the small number of patients, the results do not support the hypothesis of beneficial early treatment with nimodipine. We conclude that the scientific data that are currently available do not support routine administration of nimodipine or any other voltage-sensitive calcium channel antagonist in patients with ischemic stroke.

Acknowledgments
This study was supported by the Dutch Prevention Fund (grant 28-2467). Dr Limburg is a Clinical Investigator of the Netherlands Heart Foundation (D 93.014). Trial medication was provided by Bayer AG, Germany.

References


Very Early Nimodipine Use in Stroke (VENUS): A Randomized, Double-Blind, Placebo-Controlled Trial
J. Horn, R. J. de Haan, M. Vermeulen and M. Limburg

Stroke. 2001;32:461-465
doi: 10.1161/01.STR.32.2.461
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/32/2/461

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/